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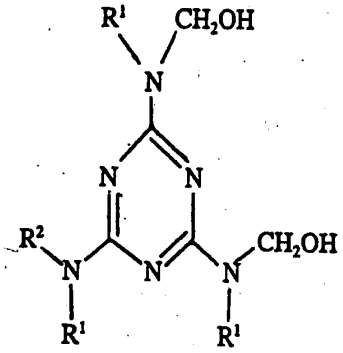
Published
With international search report.

(54) Title: MELAMINE DERIVATIVES FOR USE IN THE TREATMENT OF CANCER



(I)

(57) Abstract

The present invention provides compounds of general formula (I) wherein each R^1, which may be the same or different, is hydrogen, alkyl or an electron withdrawing group, R^2 is hydrogen, alkyl or an electron withdrawing organic group. The compounds are analogues of trimelamol which have comparable activity but enhanced stability, and are useful as anticancer agents, particularly against ovarian carcinomas.

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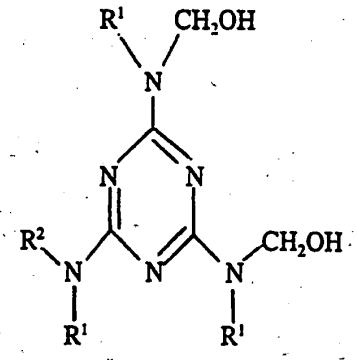
Melamine derivatives for use in the treatment of cancer

This invention relates to novel 2,4,6-triamino-1,3,5-triazines, compositions containing them, processes for making them and their use in the treatment of carcinomas, particularly ovarian carcinomas.

Trimelamol [2,4,6-tris{(hydroxymethyl) (methyl) amino)-1,3,5-triazine] is clinically active, particularly against ovarian carcinomas, but its clinical development has been halted due to difficulties with formulation due to instability with respect to the formation of dimers during formulation. It has been established that the half-life of trimelamol activity in humans is short and that may limit its clinical efficacy (I.R. Judson, *et al* Cancer Res. 49, 5475-5479, 1989). We believe that this is, in part, due to the chemical instability of the N-hydroxymethyl functions resulting in the release of formaldehyde. We have investigated reducing the number of N-hydroxymethyl functions and stabilizing these functions using electron-withdrawing organic groups (defined in the present context as electron-withdrawing relative to methyl), with a view to lengthening the half-life and also improving amenability to formulation, for example in aqueous solutions.

Accordingly this invention provides novel 2,4,6-triamino-1,3,5-triazines having the following general formula:



I

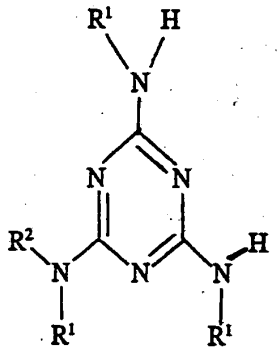
wherein each R^1 which may be the same or different, is hydrogen, alkyl or an electron-withdrawing group and R^2 is hydrogen, alkyl or an electron-withdrawing organic group. Preferably, all three groups R^1 are not hydrogen. The alkyl group R^1 and/or R^2 is preferably

a C_1-C_4 alkyl group, particularly methyl and it is preferred that all three R^1 groups, when alkyl, are all methyl.

Preferred electron-withdrawing organic groups are $-CH_2CF_3$ and $-CH_2C\equiv CH$. Because of the greater stability conferred on such compounds by the presence of such electron withdrawing substituents, which may constitute in lengthening the half-life and also in improving amenability to formulation, they may be prepared by allowing tris-hydroxymethyl compounds or precursors thereof to decompose in aqueous organic media and separating from the mixture of products (see Fig. 1) thus generated the appropriate compounds of the present invention, for example by chromatography on silica gel.

We have found that these new analogues of trimelamol have a similar level of activity against carcinomas, particularly ovarian carcinomas, as trimelamol, but are more stable and do not form dimers and polymers and thus are more amenable to formulation.

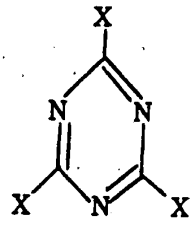
The compounds of the present invention are also prepared via novel intermediate compounds of the general formula:



II

wherein R^1 and R^2 are as defined above for the formula I

The intermediates are prepared by reacting a cyanuric halide of general formula:



III

wherein X is fluoro or chloro

with an amine of the formula R^1-NH_2 or $R^1R^2NH_2$, wherein R^1 and R^2 are as defined in formula (I), optionally in the presence of caesium fluoride.

In the absence of caesium fluoride, less than three of the substituents on the 1,3,5-triazine ring may be displaced, which allows for the preparation of asymmetrical compounds.

Treatment of the intermediates II with aqueous formaldehyde, optionally in the presence of potassium carbonate, gives the compounds of formula (I). In order to provide compounds of the formula I in which R^1 is methyl and R^2 is hydrogen, starting from compounds of the formula II in which R^1 and R^2 are also methyl and hydrogen respectively, we prefer to use a concentration of formaldehyde of from about 2 to 5% (w/v), for example about 3% (w/v). This provides a final product which contains as the major product the compound of the formula I. A small amount of the corresponding trimelamol (i.e. R^1=methyl, R^2=CH_2OH) and 'monomelamol' (i.e. three methyls but only one hydroxymethyl group) compounds will be produced. The presence of these compounds does not significantly affect the activity of the preparation of the compound of the invention in biological assays. However, if desired, the purity of the preparation may be increased by recrystallisation. For example, the material may be dissolved in methanol-water (eg at a ratio of 9:1), and recrystallised.

The compounds of this invention are biologically active and are of use against ovarian carcinomas, particularly against cisplatin-resistant ovarian carcinomas.

Also included within the scope of the present invention are pharmaceutical compositions which comprise, as active ingredient, at least one compound of general formula I, in association with a pharmaceutically acceptable carrier or diluent.

The compounds of the invention will normally be administered orally or by injection.

Compositions for parenteral administration will normally be solutions in aqueous saline, which is pyrogen free for human use. Such compositions can be administered intravenously or intraperitoneally.

Compositions for oral administration will mostly be in solid or liquid form, mostly as tablets, capsules, lozenges, etc. Liquid compositions can be solutions or dispersions in aqueous or non-aqueous media. Ideal solutions are of neutral or alkaline pH and of low ionic strength e.g. 5% dextrose.

Suitable daily doses of the compounds of the invention in therapeutic treatment of the human or animal body range from about 100mg to 3g/m^2 body-surface.

The following Examples illustrate the preparation of the compounds of the present invention.

Example 1

2,4-Bis[(hydroxymethyl) (methyl) amino]-6-methylamino-1,3,5-triazine

To a 3% w/v aqueous solution of formaldehyde (15 ml) was added potassium carbonate (691 mg, 5 mmol) then trimethylmelamine (841 mg, 5 mmol). The reaction mixture was stirred at room temperature until the initially clear solution (pH 11.5) became cloudy (2-3 h) then set aside overnight (16 h). The white granular solid which separated was recovered by filtration, washed with water (4 x 5 ml) and the product dried *in vacuo* over anhydrous $CaCl_2$. Yield 593 mg (52%); ^{1}H-NMR spectrum δ_H (Me_2SO-d_6) 2.75 (app d, 3, $HNCH_3$), 4.99 (br s, 4, $HOCH_2$), 5.36 (br s, 2, OH) 6.61 (br s, 1, NH); mass spectrum (FAB; glycerol/thioglycerol matrix) m/z 229 ($[M+H]^+$, 70%), 211 (229-H_2O, 100%), 199 (229-CH_2O, 35%), 181 (199-H_2O, 50%), 169 (199-CH_2O, 30%). Anal. $C_8H_{16}N_6O_2$ requires C, 42.10; H, 7.07; N, 36.82: found C, 41.87; H, 7.01; N, 36.55%.

In the Examples which follow, this compound is referred to as CB7646.

Example 2

Further purification of title compound of Example 1.

Using the procedures described in Example 1 above, but with 10 times the amount of starting materials, 6.325 g of product was obtained. HPLC analysis revealed the preparation to have the following composition:
title compound: 65%, trimelamol 22%, monohydroxymethyl derivative 12%.

This material (3 g) was dissolved in methanol-water, 9:1 (100 ml) at 37°C and cooled at -20°C for 24 h. The white crystalline solid was recovered by rapid filtration and dried *in vacuo* over anhydrous $CaCl_2$ to give 1.37 g of material having the following composition: title compound 87% trimelamol 4%, monohydroxymethyl derivative 9%. Signals in the ^{1}H-NMR spectrum (D_2O, determined at 37°C) were: title compound δ 3.08 ($HNCH_3$), 3.30

($HOCH_2NCH_3$), 5.29 ($HOCH_2$); trimelamol 3.33 and 5.32; monohydroxymethyl derivative 3.05, 3.27 and 5.26.

Example 3

2,4-Bis[(hydroxymethyl)(2,2,2-trifluoroethyl)amino]-6-(2,2,2-trifluoroethyl)amino-1,3,5-triazine

A solution of 2-[([hydroxymethoxy]methyl)(2,2,2-trifluoroethyl)amino]-4,6-bis (hydroxymethyl) (2,2,2-trifluoroethyl) amino-1,3,5-triazine (500 mg, 1.02 mmol) in a mixture of acetone (3 ml) and water (2 ml) was set aside at room temperature for 18 h. Acetone was removed under vacuum and the organic materials were extracted with diethyl ether.

The organic phase was concentrated and applied to a column (50 g, 3 cm dia.) of silica gel (Merck, Art. No. 9385) which was eluted with diethyl ether. There was successively eluted 2-[(hydroxymethyl)(2,2,2-trifluoroethyl)amino]-4,6-bis [2,2,2-trifluoroethyl)amino]-1,3,5-triazine (23 mg), the title compound (144 mg, 33% yield) and 2,4,6-tris [(hydroxymethyl) (2,2,2-trifluoroethyl) amino] 1,3,5-triazine (111 mg). The title compound is obtained as a white solid by trituration of the appropriate fractions with ice-cold water, recovery by filtration and desiccation *in vacuo* over calcium chloride. NMR spectrum: δ_H (Me_2SO-d_6) 4.09 (brq, 2, F_3CCH_2NH), 4.41 (brq, 4, $F_3CCH_2NCH_2OH$) 5.06 (d, 4, J=7.1Hz, CH_2OH), 5.78 (brs, 2, OH), 7.80 (brs, 1, NH). δ_F-70.23, -70.03 (2s, 3, F_3CCH_2NH) -68.3 (s, 6, $F_3CCH_2NCH_2OH$).

In the Examples which follow, this compound is referred to as CB7683.

Example 4

Stability of Compounds of the invention.

(i) Stability in solution.

Compounds were dissolved in DMSO to a concentration of 50mM. Aliquots were then dispersed into the appropriate medium to give a final concentration of 100μM in a volume of about 10ml. The diluted preparations of trimelamol and CB7646 (see Example 1) for

HPLC analysis were stored in a water bath at 21°-24 C (to simulate room temperature) or at 37°C in water, 0.9% NaCl or 5% dextrose. Aliquots were removed from each preparation at intervals to assess their stability (i.e. half-life, $T^{1/2}$) which was measured using HPLC analysis. This entailed an isocratic elution using a mobile phase comprising 10% acetonitrile, 90% 0.05M ammonium bicarbonate. The 15 cm column was packed with C8 octyl Spherisorb material. The column was encased in a cooling cabinet which was maintained at 14-17°C. Standards of freshly prepared solutions were run throughout the analysis period by way of controls.

$T^{1/2}$ measurements were made by measurement of the disappearance of compound by decreasing peak area with time, using a Data System 450MT2 data acquisition system (Kontron Instruments, Watford, UK) linked directly to the detector on the HPLC system (set at 225 nM). $T^{1/2}$ measurements were read from a semi-logarithmic plot of peak area (y) versus time (x).

The results are shown in table 1 and indicate that CB7646 has superior stability.

TABLE 1

Compound	Medium	°C	$T^{1/2}$ (Min)
Trimelamol	deionised water pH7.5	37	120
	0.9% NaCl, pH 4.9	r.t.	273
	5% Dextrose, pH 4.0	r.t.	348
CB7646	Deionised water pH 7.5	37	180
	Deionised water pH 7.5	r.t.	1080
	0.9% NaCl, pH 5.0	r.t.	960
	5% Dextrose pH 4.0	r.t.	1320

(ii) Dimer/polymer formation in solution.

An aqueous solution of CB7646 and trimelamol in 4ml aliquots at a concentration of 4-5 mg/ml was left to stand overnight (14-16 hours) at room temperature. By the end of this period, the trimelamol solution had formed a heavy precipitate, indicative of dimer and polymer formation. Similar polymerisation of trimelamol over a period of time proved problematic during its Phase I and II clinical trials (Judson et al, 1989, Cancer Res. 49;5475-5479; Judson et al, 1991, Br. J. Cancer 63; 311-313). In contrast, preparations of CB7646 prepared in Examples 1 and 2 did not form a precipitate, indicating the monomeric form is more stable that trimelamol.

Example 5

Cytotoxicity of Compounds of the Invention

The cytotoxicity of CB7646 and CB7683 was compared with trimelamol against mammalian tumour cell lines using the MTT assay. This assay is based upon the selective ability of

living but not dead cells to reduce the tetrazolium salt MTT (3-[4,5-dimethylthiazol-2-yl]-25-diphenyl tetrazolium bromide) to purple formazan (Mosmann et al, 1983, J. Immun. Methods 65; 55-63; Carmichael et al (1987) Cancer Res. 47; 936-942). Cell lines were grown in culture with continual drug exposure. The IC_{50} values (in μm) of the compounds (i.e. concentration giving 50% inhibition of cell growth as compared with untreated control) were determined, and are shown in Table 2. Figures in parenthesis refer to standard deviation or +/- values for 2 or more measurements.

TABLE 2

CELL LINE	TRIMELAMOL	CB 7646	CB 7683
PC6	12.9 (2.7)	25.1 (2.9)	31.6(1.0)
WALKER 256	9.4 (0.5)	10.7 (0.2)	ND
H69	8.5 (2.3)	14.7 (4.9)	8.9 (1.1)
CH1	23.4 (4.4)	35.8 (13.1)	40.9 (12.0)

(ND - not done).

Cell lines used:
PC6- murine plasmacytoma
Walker 256- rat mammary carcinoma
H69 - human small cell lung cancer
CH1, 41M- human epithelial ovarian cancer

The tests on Walker 256 and H69 cells were repeated using a preparation of CB7646 prepared by the recrystallisation method of Example 2. The results were:

Walker 256 - 10.5
H69 - 16.5

Example 6

Antitumour Activity Towards the ADJ/PC6 Tumour in Mice

The anti-tumour activity of CB 7646 prepared in accordance with Example 1 against ADJ/PC6 tumour in mice were compared with that of trimelamol. An implant of $1mm^3$ of tumour was made on day 1. On day 20, animals bearing tumours of comparative size were placed into groups of 4 and treated with drug on 5 consecutive days, and then left until day 30. Tumours from the treated and controls were dissected and weighed as a measure of tumour growth. Compounds were given in 5% DMSO/dextrose.

TABLE 3

% Inhibition at various Doses

(Tumour wt as % of Control Value)

Compound	Dose (mg/kg)					
	3.25	6.25	12.5	25	50	100
CB7646	5.6	-1.0	13.7	5.6	76.8	98.0
Trimelamol	0	18.2	13.7	45.5	83.9	96.0

For CB7646 (dimelamol) the results give LD_{50} > 100mg/kg, ED_{90} 74mg/kg
Therapeutic Index (TI) > 1.4

Example 7

Example 6 was repeated to obtain more precise LD_{50} values. The LD_{50}, ED_{90} and T.I. values were calculated and shown in Table 4.

TABLE 4

COMPOUND	LD_{50} MG/KG	ED_{90} MG/KG	T.I.
TRIMELAMOL	70	24	2.9
CB 7646	142	31	4.6

Example 8

CB7646 was tested *in vivo* against ovarian cancer xenografts of the PXN65 cell line transplanted into mice, substantially in accordance with Harrap et al, Annals of Oncology, 1990, 1;65-76. PXN65 is a cisplatin-sensitive line. Mice treated with either trimelamol or CB7646 showed tumour regression within 28 days whereas in untreated controls tumour growth was uncontrolled, leading to death. The results are summarised in Table 5.

TABLE 5

Activity *in vivo* against PXN65 Xenografts

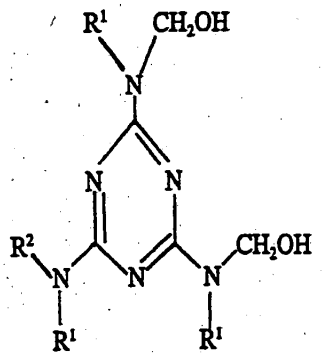
COMPOUND	Dose mg/kg	No. Doses	GD Days	Deaths
TRIMELAMOL	30 15	5 20	>273 >170	0 0
CB7646	15	20	>140	0

GD = Growth delay.

The data show that CB7646 has a comparable efficacy to trimelamol.

CLAIMS

1. A compound of general formula:



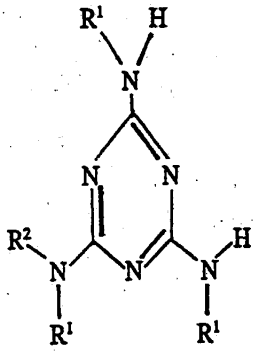
I

wherein each R^1, which may be the same or different, is hydrogen, alkyl or an electron withdrawing group, R^2 is hydrogen, alkyl or an electron withdrawing organic group.

2. A compound according to claim 1 wherein each R^1 is methyl and R^2 is H.

3. A compound according to claim 1 wherein the electron-withdrawing organic groups is CF_3CH_2- or -$CH_2C{\equiv}CH$.

4. A compound of general formula:



II

wherein R^1 and R^2 are as defined in claim 1.

5. A compound according to claim 1, 2 or 3 for use in a method of treatment of the human or animal body by therapy practised on the human or animal body.

6. A compound according to claim 1, 2 or 3 for use in a method of treatment of cisplatin-resistant ovarian cancer.

7. A pharmaceutical composition comprising an active ingredient which is a compound as defined in claim 1, 2 or 3, together with an inert diluent or carrier.

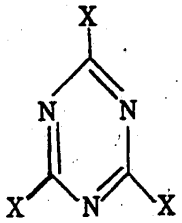
8. Use of a compound as defined in any one of claims 1, 2 or 3 in the manufacture of a medicament for the treatment of cancer.

9. A process for the preparation of a compound of formula I as defined in any one of claims 1 to 3 which comprises reacting a compound of formula II as defined in claim 4 with formaldehyde, optionally in the presence of potassium carbonate.

10. A process according to claim 9 wherein the formaldehyde is used at a concentration of from 2 to 5% (w/v).

11. A process according to claim 9 or 10 which further comprises a recrystallisation step.

12. A process for the preparation of a compound as defined in claim 4 which comprises reacting a cyanuric halide of general formula:



III

wherein X is fluoro or chloro

with an amine of the formula R^1NH_2 or $R^1R^2NH_2$ wherein R^1 and R^2 are as defined in claim 1, optionally in the presence of caesium fluoride.

13. A process according to claim 12 wherein the cyanuric halide is treated consecutively with two different amines.

14. A method of treatment of cancer which comprises administering to a patient in need of treatment an effective amount of a compound according to claim 1, 2 or 3 or a composition according to claim 7.

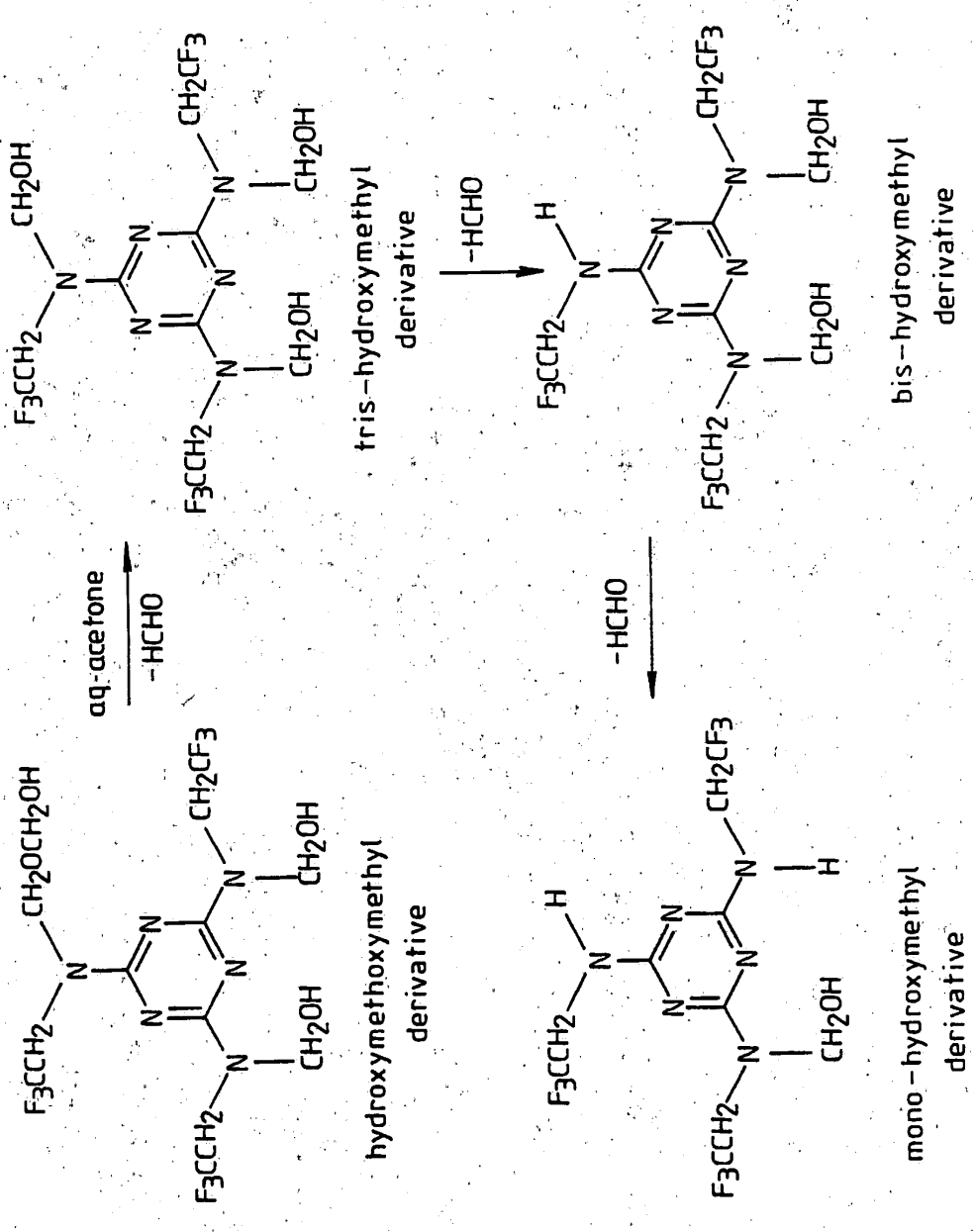

aq.-acetone
-HCHO
tris-hydroxymethyl derivative
-HCHO
bis-hydroxymethyl derivative
-HCHO
hydroxymethoxymethyl derivative
mono-hydroxymethyl derivative

Fig. 1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00625

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D251/70; A61K31/53; C07D251/64

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[10]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	CHEMICAL ABSTRACTS, vol. 114, 1991, Columbus, Ohio, US; abstract no. 253g, ARNOULD, R. ET AL. 'Compared cytotoxicity effects of five anticancer drugs on human (HBL) and mouse (B16) melanoma cells in vitro.' see abstract * RN 73702-98-4 * & 'Anticancer Res. 1990, 10(3), 789-93' ---	1,8
P,X	EP,A,0 505 220 (JARMAN M.) 23 September 1992 * complete document * -----	1-8

[10] Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
11 JUNE 1993	25. 06. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	VAN BIJLEN H.

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB93/00625

Box I Observations where certain claims were found unsearchable (Continuation f item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 14 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

./.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION C NTINUED FR M PCT/ISA/

In accordance with the reaching of the description (page 1 and 2) the compound claims 1 - 4 have been interpretetd - and searched - as containing the following restriction :" ... at least one of R_1 and for R_2 being an electron withdrawing group."

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300625
SA 72063

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 11/06/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0505220	23-09-92	AU-A- 1566792	21-10-92
		WO-A- 9216513	01-10-92